

TO THE CHAIR OF THE SCIENTIFIC JURY,
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OPINION

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Pancreatic adenocarcinoma ranks fourth as a cause of death from cancer, with survival rates ranking last compared to other types of neoplasms, and has remained unchanged for the past 40 years. The poor prognosis is due to the biology of the tumor, late diagnosis, and the lack of effective screening for early detection of this type of neoplasm. Pancreatoduodenectomy is the only treatment approach that offers a potential cure for patients with adenocarcinoma of the head of the pancreas. Despite aggressive modern techniques for intervention on borderline resectable tumors infiltrating arterial and venous trunk vessels and radical tumor resection along the portal-superior mesenteric vein axis, the celiac artery, and the mesenteric artery, after neoadjuvant chemotherapy, only ten percent of newly diagnosed patients with this pathology can undergo radical surgery at the time of diagnosis. Pancreatoduodenectomy as a multi-organ resection surgery in abdominal surgery has a morbidity rate of 18–52% and a mortality rate of less than 3%. The combination of major surgery and limited life expectancy makes quality of life extremely important for these patients. Postoperative complications are one of the leading causes of deterioration in this indicator after duodenopancreatic resection for neoplasms. Complications in percentage terms according to available literature sources are as follows: post-pancreatectomy fistula (PPF) 3–45%, delayed gastric emptying (DGE) 17.3%; post-pancreatectomy hemorrhage (PPH) 5–12%, with the choice of reconstructive technique being one of the leading causes of these complications. The technical feasibility of using pylorus-preserving pancreatoduodenectomy (, PPPD) and the appropriate choice of anastomotic technique are largely related to the postoperative exocrine function of the pancreatic remnant. Pancreatic exocrine insufficiency is a manifestation of many pancreatic diseases and is associated with a deficiency of micronutrients and fat-soluble vitamins. Enzyme replacement therapy is associated with improved survival compared to control groups of patients in numerous studies. Due to the scarce and

contradictory studies on the dynamics of pancreatic exocrine secretion after pancreatoduodenectomy for neoplasms and the lack of in-depth analysis of their relationship with the type of reconstructive technique, it is scientifically appropriate to investigate them in detail. In this context, it is appropriate to study the relationship between impaired digestion and tumor growth and metastasis in this type of carcinoma.

All this forms the subject of Dr. Nikolay Nikolov's dissertation: "FEATURES OF EXOCRINE PANCREATIC FUNCTION AFTER DUODENOPANCREATIC RESECTION FOR ADENOCARCINOMA" extremely relevant, useful, and very well chosen.

The study was conducted in two phases – retrospective and prospective, based on postoperative follow-up. A retrospective cohort study was conducted over a period of 6 years, selecting 92 patients with adenocarcinoma of the head of the pancreas for the purpose of the study.

Within the framework of the study, the author examines in detail various preoperative indicators:

1/ Assessment of performance status. This indicator is examined before and after surgery, comparing it with data from the assessment of the exocrine function of the pancreas and negative changes in average body weight. Based on this indicator, Dr. Nikolov divides patients into two groups – with good and poor status according to the scoring system.

2/ Examination of fecal elastase-1 – an enzyme that directly indicates the function of the pancreas before surgery and of the residual pancreas after surgery.

3/ Preoperative and intraoperative assessment of pancreatic exocrine function by combining laboratory analysis and imaging diagnostic methods. Fecal elastase 1 was used to assess exocrine pancreatic function preoperatively, with a sensitivity of 95–100% and a specificity of 65–95%. With a main pancreatic duct width greater than 0.3 cm, measured by CT or ultrasound, preoperative exocrine dysfunction is expected in 92% of cases.

4/ Endoscopic examination of the anatomical integrity and functional suitability of the pancreatogastric anastomosis. In cases of pancreatogastric anastomosis, endoscopic diagnosis was performed one month after the intervention to determine the frequency of anastomotic coverage with gastric mucosa. Laboratory analysis of postoperative exocrine function and its relationship to tumor spread and local recurrence. In the dissertation, the author focuses on and thoroughly examines aspects of reconstruction with regard to the performance of pancreatic anastomosis as the most critical part of the reconstruction after pancreatoduodenal resection. The surgical techniques for performing pancreaticogastric anastomosis and

pancreaticojejunal anastomosis are described in detail. The positive and negative aspects of both surgical techniques are discussed, and the correlation between the type of anastomotic technique and the intraoperatively assessed condition of the pancreatic parenchyma is very impressive. The study skillfully incorporates the criterion of palpation and intraoperative consistency of the pancreas and pancreatic remnant, and statistically and empirically studies and derives criteria for selecting a surgical technique based on this finding. Although subjective, intraoperative consistency of the pancreas is a purely practical criterion that allows the surgeon, during the course of the surgical intervention, to assess which type of reconstruction technique will give the best results intraoperatively, perioperatively, and postoperatively. The types of postoperative complications were studied in detail according to the type of postoperative pancreatitis, bleeding, and formation of pancreatic fistula, with the latter also classified according to severity according to internationally recognized classifications. Postoperative complications are classified according to the Dindo-Clavien classification. Postoperative follow-up of patients is extensive, with laboratory indicators of enzyme activity in the pancreatic remnant being examined and monitored, and endoscopic and imaging methods are used to monitor the secretory function and changes in the pancreatic resectate and its anastomosis with the gastrointestinal tract.

In the postoperative follow-up of the patient group, the positive effect of the preserved and improved postoperative function of the pancreatic remnant, which has a positive effect on postoperative survival and determines the cessation or slow development of metastasis and progression of the underlying disease. The relationship between the positive effects described above and the surgical technique used is extremely well described, which is also proven by a statistical analysis.

The positive significance of the absence of complications in the postoperative period for reducing hospital stay is clearly presented and statistically linked to the choice of surgical technique. The positive effects of pancreato-gastric anastomosis and its superiority over pancreato-jejunal anastomosis are presented in terms of the absence of complications in the early and late postoperative period, as well as in terms of survival and quality of life factors. In the postoperative follow-up, patients from the study group are followed up on a monthly and weekly basis, which makes the dissertation complete and thorough to the point of perfection.

The dissertation contains a total of 118 pages, illustrated with 39 figures and 43 tables. The bibliography includes 258 titles, of which 5 are in Cyrillic and 253 in Latin.

The aim of the dissertation is well formulated and structured. The tasks set have been fully accomplished and correspond to the parameters set in the aim. In the "Discussion" section, Dr. Nikolov analyzes his results by comparing them with those

presented in the contemporary literature, showing fully comparable and consistent results. The limiting factors and the boundaries of the study's possibilities are clearly presented, which makes the dissertation objective. The division of the group of selected patients into men and women and their descriptive and detailed follow-up according to the pre-defined study criteria is fully consistent with the current criteria of the SAGER Guidelines protocol.

Dr. Nikolov's dissertation is supported by an in-depth, focused, and logically sound statistical analysis. The statistical methods used for the purposes of the study are:

- Descriptive statistics – means, standard deviations, range, and degree of balance of the sample.
- Percentage ratios and distributions.
- Correlation analysis.
- T-test for comparison of the studied groups.
- Kaplan-Meier test for survival.

All statistical analyses were performed with a confidence interval of 95%.

In conclusion, the author shows that the exocrine function of the pancreas, in the context of resection surgery for pancreatic adenocarcinoma, is of paramount importance. Patients with normal digestion show a lower frequency of recurrence and metastasis, prolonged survival, and reduced mortality.

The choice of reconstruction technique should be made on a strictly individual basis, with the degree of pancreatic fibrosis being determined prior to surgery by imaging and intraoperatively by the surgeon's tactile sensation. This could optimize the frequency of postoperative complications and prevent further deterioration of the residual pancreas function. Taking these steps would improve quality of life, performance status, and life expectancy. In addition, improvements could be achieved in parameters such as early postoperative mortality, duration of resuscitation, and length of hospital stay. This would also benefit the financial aspects of treating this pathology. As part of the comprehensive treatment of pancreatic adenocarcinoma, enzyme replacement therapy should be routinely administered after determining fecal elastase levels.

As a result of his well-structured and well-supported conclusion, Dr. Nikolov draws six conclusions, with which I fully agree.

The dissertation concludes with five contributions that are well defended and logically derived as consequences of the scientific research process.

The three publications preceding the completion and defense of the dissertation, in which Dr. N. Nikolov is the lead author, have been reviewed.

The dissertation of Dr. Nikolay Veselinov Nikolov is well organized and illustrated. It reads very easily. It is stylistically consistent and free of spelling errors.

After reviewing Dr. Nikolay Veselinov Nikolov's dissertation in detail, I believe that the work is dissertable, innovative, and will be useful to surgeons in the country in their daily work. The author has indisputable qualities, proven in his daily surgical practice at a leading medical institution, which is why I would like to recommend that the distinguished members of the scientific jury approve it and award Dr. Nikolay Veselinov Nikolov the educational and scientific degree of "Doctor."

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